REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Status of Claims

Claims 1-30 are pending in the application. Claims 19-30 were withdrawn. Claims 1-15, 17, and 18 were rejected. Claims 1, 2, 4, 5, 9, 11, and 13-18 are amended herein. Support for this amendment can be found, at least, in the claims as filed and the page 26, lines 7-15 of the specification. In the Office Action, the Examiner withdrew claim 16 from consideration. In response, Applicants note that CFLAR recited in claim 16 is an elected subject matter in Applicants' response to restriction dated April 29, 2009 and therefore Applicants respectfully request removing the withdrawal of claim 16.

CLAIM OBJECTIONS

In the Office Action, the Examiner objected to claims 2 and 4 for containing gene symbols without their full names. In response, Applicants note that Applicants have amended these claims and the amended claims recite the full name of the genes. Therefore, Applicants respectfully request removal of this objection.

Additionally, the Examiner objected to claims 2, 4, and 9 for reciting non-elected subject matter. Specifically, the Examiner notes that the claims are allowable. The Examiner further notes that "[p]rior to the allowance of any claim, subject matter that has not been re-joined with the elected subject matter will be required to be removed from the claims. In response, Applicants hereby thank the Examiner for indicating the allowability of the claims. Applicants note that Applicants have amended claims 2, 4, and 9, and the amended claims do not recite any non-elected subject matter, and therefore Applicants respectfully request removal of this objection.

SPECIFICATION OBJECTIONS

In the Office Action, the Examiner objected to the specification for containing hyperlinks in pages 27-29 and 35 and typographical error in page 28. In response, Applicants have amended the specification herein to remove the browser executable hyperlinks and the typographical error in these pages. Therefore, Applicants respectfully request removal of these objections.

CLAIM REJECTIONS

Rejections Under 35 U.S.C § 112, Second Paragraph

In the Office Action, the Examiner rejected claims 1-15, 17, and 18 under 35 U.S.C. § 112, second paragraph, as being indefinite for omitting an essential step. Specifically, the Examiner asserts that the independent claims 1 and 16 have only a single process step of determining gene expression profile that allegedly does not render the prediction or identification of transplant rejection. Applicants respectfully disagree. However, in order to expedite the prosecution, Applicants have amended the claims and the amended claims recite the steps of "collecting a blood sample from...subject" as well as "determining a gene expression profile in said sample...compared with a standard...thereby predicting said transplant rejection in said subject." Accordingly, the amended claims contain all the essential steps and thus Applicants respectfully request withdrawal of this rejection.

Examiner also rejected claims 14, 15, 17, and 18 under 35 U.S.C. § 112, second paragraph, as further being indefinite. Specifically, the Examiner asserts that these claims contain incorrect dependency by reciting the terms "the method of claim 15." In response, Applicants have amended these claims and the amended claims contain correct dependency. Therefore, Applicants respectfully request withdrawal of this rejection.

Rejections Under 35 U.S.C § 112, First Paragraph

In the Office Action, the Examiner rejected claims 1-13 under 35 U.S.C. § 112, first paragraph, as failing to comply with enablement requirement. Specifically, the Examiner asserts that the specification does not disclose definite expression levels for a standard, and they are unpredictable and thus require undue experimentation. Applicants respectfully traverse this rejection.

Applicants note that Applicants have amended claims and amended claim 1 is directed to "[a] method for predicting a cardiac transplant rejection in a human subject, comprising: collecting a blood sample from said subject; determining a gene expression profile in said sample, wherein said gene expression profile comprises increased expression of at least 4 genes as **compared to a standard**, and diminished expression of at least one gene, as **compared to said standard**, wherein one of said at least 4 genes is an ubiquinol-cytochrome c reductase binding protein (*UQCRB*), thereby predicting said transplant rejection in said subject." [emphasis added]. The specification fully enables one of skill in the art to ascertain these upper and lower limits.

For example, the specification demonstrates multiple methods of determining the amount of gene expression and explains numerous statistical tools for correlating the values with transplant rejection. *See* page 6, lines 22-27 and page 8, line 27 through page 9, line 4 of the specification. In particular, Example 1 shows expression data from microarray method as well as qRT-PCR method. *See* page 27, lines 7-27 and page 29, lines 10-22. Form these test data, it is merely a routine statistical task for one of skill in the art to identify a standard value for comparison so as to determine prediction or identification of transplant rejection, as claimed.

In addition, the specification describes selecting patient population and analyzing data using various statistical tools. *See* page 26, lines 4-5 and 18-28, page 28 line 20 through page 29, line 7, and figures 1-4. Specifically, the specification explains as follows:

> The probability of selecting a set of 91 candidates by chance was estimated. 91 genes were randomly selected, a determination of gene concordance was made, with the total number of concordant genes in the randomly selected group computed. This process was repeated 10000 times, and a p-value was determined, reflecting the probability of a chance occurrence of the observed or better concordance... Cluster Analysis...The capacity of candidate markers to distinguish Control, Rejection, and Post-Rejection samples was assessed using hierarchical clustering. Clusters were constructed using average linkage clustering and Pearson correlation coefficients as a measure of similarity using Cluster software and displayed using Treeview software.

See page 28 line 20 through page 29, line 7.

Accordingly, the specification provides an example of a statistical selections, correlations, and statistical-significance (p) values. Additionally, the specification explains a standard as follows:

> "[S]tandard" may refer to a pooled sample of successful recipients for the same organ transplant. In another embodiment, standard may be ethnically- or gender- or age-matched recipients. It is to be understood that the standard may be derived from any subject, or pool of subjects, whose expression profile or profiles, once generated, is sufficient to detect even minute relative differences in expression, when compared to a potential transplant recipient, or in another embodiment, transplant recipient.
>
> "[C]ompared to a standard", refers to relative changes in expression where the standard is derived from a single individual, or is derived from pooled subjects who have successfully undergone a transplant. In another embodiment, a standard can be derived from a single subject following about 1 to about 5 years of having undergone successful transplantion. In one embodiment, a standard can be derived from a subject who has undergone transplant of the specific tissue for which the subject is being evaluated, such as, for example, being obtained from a subject having undergone a successful cardiac transplant. In another embodiment, the standard is derived from a subject who has undergone transplant of a different tissue type than that sought by the recipient, however, the two individuals, or pool of individuals are of a similar genetic background.

See page 9, lines 7-13 and page 10, lines 6-16 of the specification.

Clearly, the specification teaches one of skill in the art how to identify the values of a standard for comparison of expression levels.

Only the most basic and routine task would therefore be required in order to obtain a standard value. This is greatly underscored when taking into account that statistical tools for identifying the standards were well known in the art and also explained in the specification, as set forth above.

Furthermore, the Examiner has failed to set forth a case that undue experimentation would be required to practice the invention across the full scope of the instant claims. It is the Examiner that bears the burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by a claim is not adequately enabled by the description of the invention in the specification. *In re Wright*, 9 U.S.P.Q.2d 1510, 1512-1513 (Fed. Cir. 1993) (citing *In re Marzocchi*, 169 U.S.P.Q. 367, 369-70 (CCPA 1971)).

The Examiner has provided no sufficient basis to doubt the enablement of the instant claims. Rather, the Examiner notes that "the claims encompass detecting any level of gene expression in a sample from an individual and comparing that level to any control level or average level to determine an elevated that is indicative of rejection." *See* Office Action, page 9, lines 11-15. In response, Applicants note that claims are directed to comparing the expression level to standard and as discussed above it is well known and routine in the art to apply statistics on different values of raw data to determine their significance and thereby identify a threshold limit of a standard. Statistical methods are well known and also explained throughout the specification, as discussed above. While some statistical testing may be necessary to compare to standard, such test for data on mere five genes is not undue.

The above-discussed teachings in Applicants' specification are more than adequate to enable the full scope of the invention and cannot properly be ignored. While Applicants acknowledge this would require some routine testing and statistical analysis, "[e]nablement is not precluded by the necessity for some experimentation such as routine [testing]." *In re Wands*, 858 F.2d at 737. Some amount of experimentation is permissible, especially when the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* (quoting *Ex parte Jackson*, 217 USPQ 2d 804, 807 (Bd. App. 1982)). Such is the case here, where

only routine testing is required and extensive guidance is provided. Additionally, the experimentation described by Applicants is inarguably typical in the art, and not undue. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165 at 1174.

Finally, Applicants need not disclose all possible values of the expression levels. The legal standard for enablement does not require that Applicants demonstrate enablement for all possible claimed iterations. Enablement must bear only a reasonable relationship to the scope of the claims. *See* MPEP 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970)). For example, a patent applicant is not required to "predict every possible variation, improvement or commercial embodiment of his invention." *United States Steel Corp. v. Phillips Petroleum Co.*, 673 F. Supp. 1278, 1292 (D. Del. 1987), *aff'd,* 865 F.2d 1247, 1250 (Fed. Cir. 1989) (specifically quoting this statement).

Accordingly, the withdrawal of the rejection under 35 U.S.C. §112, first paragraph for lack of enablement is respectfully requested.

Rejections Under 35 U.S.C § 102

In the Office Action, the Examiner rejected claims 1, 3, 5, and 10-12 under 35 U.S.C. § 102(b) as allegedly being anticipated by Ma *et al.* (WO 2001/81916) ("Ma"). Specifically, the Examiner asserts that Ma teaches methods of detecting transplant rejection that include four over-expressed genes and one under-expressed gene. Thus, the Examiner finds that Ma anticipates the claimed invention. Applicants respectfully disagree.

Applicants note that Applicants have the claims. The amended claims recite "one of said at least 4 genes is an ubiquinol-cytochrome c reductase binding protein (*UQCRB*)." Nowhere does Ma disclose, teach or suggest UQCRB. Rather, Ma relates generally to detecting immune activation genes such as perforin (P), granzyme B (GB), and Fas ligand (FasL). Since Ma does not disclose UQCRB, Ma does not anticipate the claimed invention and therefore Applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

Mark S. Cohen
Attorney/Agent for Applicant(s)
Registration No. 42,425

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Pearl Cohen Zedek Latzer, LLP
1500 Broadway, 12th Floor
New York, New York 10036
Tel: (646) 878-0800
Fax: (646) 878-0801